REMARKS

1. Claim Rejection – 35 U.S.C. § 102(b)

Claims 1-6, 11-15 and 20-22 stand rejected under 35 U.S.C. § 102(b) ("Section 102(b)") as being anticipated by United States Patent No. 4,963,360 to Argaud ("Argaud"). Applicant respectfully traverses this ground of rejection.

An invention is unpatentable under 35 U.S.C. § 102(b) if "the invention was patented or described in a printed publication . . . more than one year prior to the date of application for patent in the United States." A 35 U.S.C. § 102(b) rejection is only appropriate where "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999); M.P.E.P. § 2131. In addition, "the identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); *M.P.E.P.* § 2131. For the reasons set forth below, Applicant submits that the reference cited by the Examiner neither teaches each and every element of the claimed invention, nor shows the identical invention in as complete detail as in Applicant's claims, and thus does not anticipate the present invention.

The dermal administration of pharmaceutically active compounds has long been known in the practice of medicine, and continues to be an important technique in the delivery of pharmaceutically active compounds. It is known that elevated temperature can increase the absorption of drugs through the skin—this much Argaud taught or applied. What was still needed was an improved drug administration system. More specifically dermal drug delivery systems needed to be more flexible, controllable and titratable to better accommodate various clinical needs.

Delivering a specific therapeutic range of a pharmaceutical is critical to clinical efficacy, and ensuring patient safety. Patient overdose is a serious danger that requires precise control of the intensity and duration of heat when pharmaceuticals are administered by a heated dermal apparatus. Alternatively, insufficient intensity and duration of heat applied to systems for dermal administration of a pharmaceutical results in the pharmaceutical being administered below its therapeutic range, which provides little or no benefit to the patient. Therefore, it is important to control the intensity and duration of heat precisely.

Argaud teaches an uncontrolled heating source with no mechanism for limiting the duration of time to a predetermined safe duration, or for strictly limiting the amount of heat that is generated in the exothermic reaction. Argaud teaches an exothermic package, which provides heat when exposed to air, attached to a layer that carries medicine, to enhance absorption of medicine through the skin. Argaud further describes the contents of the carrier layer and the exothermic layer providing examples of each. That is all that Argaud teaches. The concept of "control" is absent form Argaud's teachings. Argaud does not teach preparing and deciding beforehand what the appropriate dosage should be. Argaud neither actively controls the surface area's exposure to oxygen, the exothermic medium's shape, nor the amount of heat generated. Argaud did not indicate potent or particularly dangerous drugs because there is significant risk of overdose when using an uncontrolled heat source to increase the absorption of drug through the skin. When used with more potent drugs, such as those drugs used in the present invention it would only be safe to use heat if the amount of heat and the duration of heat could be strictly controlled. *Specification, p. 37, lines 23-29 and p. 38, lines 1-5.*

While Argaud discloses an apparatus capable of increasing drug administration rates, the apparatus itself fails to implement any feature that enables specific temperature regulation capable of precisely controlling and possibly reducing rates of drug delivery, as claimed by the present invention. Oxygen is the fuel that allows the exothermic reaction to occur that increases the temperature of the exothermic packaging body. But Argaud does not teach that the amount of air supplied to the exothermic layer would determine the temperature and duration of heat caused by the exothermic layer. More critically, Argaud does not teach any means of regulating the rate at which oxygen interacts exothermically with the exothermic layer of the package. Argaud does not teach that a user may control the amount of heat applied by the exothermic package body by varying the duration of time that that package is exposed to oxygen; neither does Argaud teach that the amount of heat applied could be varied by the duration of time that the package is applied to the patient of interest. Certainly, Argaud does not teach a package body itself that is capable of controlling the magnitude and duration of heat produced by the package.

A package body capable of controlling the magnitude and duration of heat is not inherent in Argaud's disclosure. Where oxygen is the limiting reagent it might be tempting to assume that with increased duration of exposure to oxygen the exothermic layer will produce more heat for a longer period of time. Additionally, it might be tempting to assume that with more exothermic reagent placed in the exothermic layer, more heat would be produced for a longer period of time. These simplifying assumptions are flawed. The amount of heat produced, and the duration of the reaction in this case are complicated by factors beyond oxygen being the limiting reagent. One such complicating factor is proximity. Oxygen is only exposed to the exothermic reaction along the surface area of the exothermic reactants. As additional exothermic reagent is added to the package the volume of the package increases at a cubed rate, while the surface area of the

package increased at a squared rate, of which only a portion is exposed to oxygen. The remainder does not react. Thus, increased volumes of reactants placed in the exothermic package do not correlate directly with changes in intensity and duration of heat produced, providing an unreliable and less predictable means of affecting intensity and duration of heat produced. Because these simplifying assumption are unreliable, Argaud fails to disclose a temperature modification apparatus capable of achieving selective, precise, on-demand delivery of an analgesic through the skin, as claimed by the present application. Even if the simplifying assumptions produced reliable results it would be inappropriate to impute those assumptions into Argaud's disclosure; Argaud does not teach the principle of control.

As the present application indicates, drug absorption rates depend on a number of factors, each of which must be precisely regulated to enable rapid and effective drug administration while preventing drug overdose. Regulating the intensity of heat and duration that heat is produced by such unquantified means could produce deadly or ineffective results when administering pharmaceuticals that have specific therapeutic ranges. So, while simplifying assumptions produce the illusion that the Argaud patch could be removed from the skin to decrease the intensity or duration of heat, Argaud does not teach any other methods for modifying the intensity or duration of heat produced. Argaud is simply an on-off-switch; the Argaud patch is exposed to air or not. Argaud does not teach controlled air flow.

The present application teaches what Argaud does not. The present invention teaches methods that would allow manufacturers to produce heat patches that have predetermined temperature ranges and predetermined times that the patches would produce heat. Additionally, the present invention teaches that the predetermined temperature ranges and times could be modified by those administering the patch by means other than adding or removing the patch.

The present invention claims "a method of *controlled* delivery of analgesic" (emphasis added) comprising a "temperature modification apparatus designed to deliver a particular dose of a drug at a pre-determined temperature range for a pre-determined duration of time, to deliver an appropriate amount of the drug." See *Claim 1.* In addition, the present invention claims "a temperature control apparatus secured to said patch, said temperature control apparatus being capable of heating said patch and said patient's skin proximate said patch to a pre-determined range for a predetermined duration of time." See *Claim 22.*

> The present invention is specifically engineered to provide a *predetermined* amount of heat for a *predetermined* time, thus precisely controlling the dosage of medicine administered to a given patient. Based on experimental data, the temperature modification apparatus has been designed to deliver *precise control* over intensity and duration of heat produced. One embodiment of a *controlled* heat generating apparatus is a shallow chamber including non-air permeable side wall(s), a bottom wall, and a non-air permeable top wall which has area(s) with limited and desired air permeability (e.g., holes covered with a micro porous membrane)... *The desired heating temperature and duration can be obtained by selecting the air exposure of the top (e.g., selecting the right size and number of holes on the cover and/or selecting the micro porous membrane covering the holes for a specific air permeability), and/or by selecting the right quantities and/or ratios of components of the heat generating medium.* (emphasis added) *Specification, page 13 lines 24-27 and page 14 lines 5-10.*

The "method of controlled delivery" of claim 1 and the "temperature control apparatus" of claim 22 result in a closed system, whereas Argaud is an open system; basic scientific principles are based on the benefits of control provided by closed systems. Because the present invention utilized non-air permeable barriers the amount of oxygen that enters the system is controlled, whereas in the open system of Argaud, oxygen enters uncontrolled into the system. Where Argaud is an exothermic reaction in an air permeable bag completely exposed to oxygen, the present invention is a titrated exothermic reaction tightly separated from oxygen by air impermeable barriers. The titrated closed system, isolated from the limiting reagent, is exposed with mathematical precision to oxygen by carefully controlling specific parameters: "selecting

the right size and number of holes on the cover and/or selecting the micro porous membrane and covering the holes for specific air permeability, and/or by selecting the right quantities and/or ratios of components of the heat generating medium." *Specification*, page 13 lines 24-27 and page 14 lines 5-10. Since the amount of heat generated is determined by the amount of surface area exposed to oxygen, the amount of heat generated can be varied by embodiments of the present invention as the amount of surface area exposed to oxygen is varied. Thus, by varying the amount of surface area exposed to oxygen, the amount of heat generated is controlled.

The detailed description of the illustrated embodiments provides significant scientific data regarding the size and number of holes used to produce specific temperatures for specific durations of time. *Examples 1-28 in the Specification, pages 21-64.* The ability of the present invention to control the time and rate at which the system and method generates heat allows for the improved administration of analgesics. As disclosed in the many examples of Applicant's specification, the temperature modification apparatus is capable of administering analgesics over both a long period of time, such as the 240 minutes disclosed in Example 1, and over a short period of time, such as the 15 minutes disclosed in Example 3. *Specification, page 32, lines 1-3.* In addition, the temperature modification apparatus is capable of keeping the skin temperature within various selected ranges. *Specification, page 22, lines 25-26; page 34, lines 18-20.* The ability to control the temperature rage and duration of time improves the administration of analgesics by more effectively treating a variety of pains, illnesses, injuries and addictions, including localized pain, nicotine addiction, athletic injuries, cancer pain, inflammations, hypertension, depression, diabetes, migraines, asthma, obesity, and nausea. This ability to control is particularly helpful in customizing treatments, especially because different people react differently to the same drugs. Exercising accurate control over the drug delivery process is

essential to the safety and health of the patient. The Office has not shown these limitations in Argaud.

Based on the foregoing, Applicant respectfully submits that Argaud does not anticipate any of the claims of the present invention. As such, Applicant respectfully requests that the rejection under 35 U.S.C. § 102 be withdrawn.

Dependent claims 2-6, 11-15, and 20-22 place further limitations on what is otherwise argued allowable subject matter. Therefore, Applicant respectfully submits that these claims stand in a condition for allowance.

2. Claim Rejection – 35 U.S.C. § 103(a)

Claims 1, 19 and 23 stand rejected under 35 U.S.C. §103(a) ("Section 103(a)") as obvious in view of Argaud. An invention is unpatentable under Section 103(a) "if the differences between the subject matter sought to be patented over the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains." To establish a *prima facie* case of obviousness, three criteria must be met. "First, there must be some suggestion or motivation . . . to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2142. For the reasons set forth below, Applicant submits that the reference cited by the Office neither provides a suggestion or motivation to modify, nor does the prior art teach all of the claim limitations, and thus does not anticipate the present invention.

The Examiner relied on Argaud to establish the §103 rejection. As previously discussed a comparison of Argaud and the present invention shows important differences. The "method of

controlled delivery" claim 1 and the "temperature control apparatus" of claim 22 result in a closed system, whereas Argaud is an open system. In the closed system of the present invention, the amount of oxygen that enters the system is actively controlled, whereas in the open system of Argaud, the entry of oxygen enters uncontrolled into the system. Since the intensity and duration of generated is determined, in part, by the amount of surface area exposed to oxygen, the amount of heat generated can be varied by embodiments of the present invention as the amount of surface area exposed to oxygen is varied. Thus, by varying the amount of surface area exposed to oxygen, the amount of heat generated is controlled. In contrast to the controlled exposure to oxygen in the present invention, Argaud teaches the uncontrolled exposure to oxygen as oxygen freely enters through the air-permeable film. *Argaud, Claims 1 and 3.* Consequently, Argaud neither actively controls the surface area's exposure to oxygen, the exothermic medium's shape, nor the amount of heat generated.

One skilled in the art would not have been motivated to control the delivery of the medicinal component because no control mechanism existed to modify the exposure to oxygen. In fact, it is an impermissible form of hindsight analysis to presume that the Arguad reference taught that one could control the intensity and duration of heat by varying the quantity of exothermic medium utilized. Arguad does not teach or suggest the claim limitation of controlling the intensity or duration of heat generated in any fashion. Particularly, Arguad does not disclose, nor is there any discussion regarding varying the quantity of exothermic medium utilized for a given patch.

As discussed above, claim 1 as amended, recites "a temperature modification apparatus capable of controlling and selectively modifying a magnitude and duration of heat to achieve

selective, precise, on-demand delivery of said analgesic through said skin." Applicant finds no mention or suggestion of these elements in the cited references, nor any equivalent thereof.

Indeed, although Argaud discloses an apparatus capable of increasing drug absorption performance, Argaud neither discloses nor suggests an apparatus having a temperature regulation system that achieves selective, precise, on-demand drug delivery, as claimed by the present application. Instead, Argaud emphasizes the ability of the exothermic layer to develop heat when brought into contact with air, thereby increasing drug delivery rates. Argaud, however, fails to mention or suggest that the apparatus may control, and possibly limit, such drug delivery rates.

Finally, Applicant respectfully submits that claim 23, which claims the "step of applying a temperature modification apparatus proximate to said delivery site on said skin" that is "performed when said patient starts to feel the onset of breakthrough pain," is not obvious because of the control and speed required for effective treatment after the onset of breakthrough pain. This is evident in one disclosed embodiment of the present invention where a non-air permeable top wall with holes is used to control the rate of drug delivery. See *Specification, page 20, lines 20-21.* One way the present invention functions to increase the rate at which the drug is delivered is to uncover additional holes, exposing the exothermic layer to more oxygen, which in turn raises the temperature and increases the rate at which the drug is delivered.

Applicant respectfully submits that Argaud does not teach or suggest the limitations taught in claims 1, 9 and 23 discussed above. In particular, one skilled in the art of analgesic administration would not think to introduce the control of the present invention.

Accordingly, Applicant respectfully requests withdrawal of the Examiner's rejections of claims 1, 9 and 23 as obvious in view of Argaud under Section 103(a).

CONCLUSION

Applicants submit that the claims are now in condition for allowance. Accordingly, Applicants request favorable reconsideration. If the Examiner has any questions or concerns regarding this communication, the Examiner is invited to call the undersigned.

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